REMARKS

Claims 1 and 15-28 are currently pending in this application. Claims 1 and 15-28 have been examined and stand rejected on arguments laid out in the Final Office Action mailed on November 21, 2006. Applicant thanks for Examiner for the careful examination of this case, and respectfully requests reexamination and reconsideration of the case, as amended.

No new matter is added to this case by the present Response. Applicant is submitting the presence Response without prejudice to the subsequent prosecution of claims to some or all of the subject matter which might be lost by virtue of this paper, and explicitly reserves the right to pursue some or all of such subject matter, in Divisional or Continuation Applications.

Below Applicant addresses each of the rejections levied in the Office Action and explains why the rejections are not applicable to the pending claims.

Claim Objection – Double Patenting

The Examiner advised that claim 28 will be objected to under 37 C.F.R. § 1.75 as being a substantial duplicate of claim 22 should claim 22 be found allowable; claim 26 and 27 will be objected to under 37 C.F.R. § 1.75 as being a substantial duplicate of claim 1 should claim 1 be found allowable; and claim 21 would be objected to under 37 C.F.R. § 1.75 as being a substantial duplicate of claim 20 should claim 20 be allowable.

Applicant appreciates the Examiner's advisement, and respectfully submits that any or all of the above objections will be addressed and/or explained upon indication of allowability of the Claims.

Claim Rejections – 35 U.S.C. § 112

Claims 1 and 15-28 remain rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. In particular, in the Office Action, the Examiner states that "the specification fails to provide adequate guidance and evidence for how to treat various neuroectodermal tumors in the brain by using a pharmaceutical composition comprising a chlorotoxin fused to any cytotoxic moiety *via* various administration routes so as to provide therapeutic effect *in vivo*"

Applicant disagrees and respectfully submits that the proper relevant legal standard for establishing (and enabling) utility with regard to a pharmaceutical property is set out in *In re Brana*, 51 F. 3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). Although *Brana* is primarily styled as a case for the establishment of a practical utility (because the rejection at issue in that case was so styled), its holdings are equally applicable to the "how to use" branch of enablement and therefore are controlling in the present instance. Indeed, the *Brana* decision itself acknowledges the relationship, noting that the requirement that an invention have utility is found in 35 USC § 101 but is also implicit in Section § 112 because "if a claimed invention does not have utility, the specification cannot enable one to use it" (51 F.3d 1564). Thus, it is clear that the *Brana* court was addressing *both* whether the specification asserted a utility *and* whether it taught how to use the invention.

In *Brana*, the court held that:

> "proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility."

(51 F. 3d 1567). The court explained its holding by stating:

> "We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans"

(51 F. 3d 1567).

The facts in *In re Brana* are relevant to this case. The patent application at issue in *In re Brana* related to particular compounds for use as antitumor substances. The specification included illustrated the cytotoxicity of the compounds against human tumor cells *in vitro*. Furthermore, the Applicant in *In re Brana* submitted a Declaration including test results showing that several compounds within the scope of the claims exhibited significant antitumor activity against the L1210 standard tumor model *in vivo*. Nonetheless, the Examiner rejected the claims

on the ground that the specification failed to describe any specific disease against which the claimed compounds were active. The court held this evidence to be sufficient.

In the present case, the claims relate to methods of treating an individual having a neuroectodermal tumor by administering an effective dose of chlorotoxin fused to a cytotoxic moiety, and are rejected, as noted above, on the ground that "the specification fails to provide adequate guidance and evidence for how to treat various neuroectodermal tumors in the brain by using a pharmaceutical composition comprising a chlorotoxin fused to any cytotoxic moiety *via* various administration routes so as to provide therapeutic effect *in vivo*". Thus, the situation is highly analogous to that present in *Brana*.

As in *Brana*, the specification in the present case provides *in vitro* evidence of efficacy of exemplary claimed compounds. For example, Examples 8-17 of the Application, as filed, report experiments in which more than 250 frozen or paraffin sections of human biopsy tissues were histochemically stained with TM-602 (a chemically synthesized form of chlorotoxin covalently linked to a biotin group). The results obtained in these experiments show the specific binding of TM-601 to tissues from 18 different neuroectodermally derived tumors (*i.e.*, from WHO grade IV: glioblastoma multiforms, WHO grade III: anaplastic astrocytoma, WHO grade II: low grade, WHO grade I: pliocytic astrocytoma, oligodendrogliomas, other glioamas, gangliomas, meningiomas, ependymomas, metastatic tumors in the brain, edulloblastomas, neuroblastomas, ganglioneuromas, pheochromocytomas, peripheral primitive neuroectodermal tumors, small cell carcinoma of the lung, Ewing's sarcoma, and melanomas, which represents the entire list of tumors presented in claims 16-20). Based on these results, an assertion is made in the Specification that chlorotoxin-derived molecules can be utilized to target specifically for therapeutic or diagnosis purposes neuroectodermal tumors (see second paragraph of Example 17 of the Application, as filed), and that for such purposes, chlorotoxin linkage of radioactive molecules or cytotoxic moieties, such as saporin, could be employed (see last sentence of Example 2 of the Application, as filed). Thus, the Specification explicitly teaches, and one of ordinary skill in the art would understand, that binding of chlorotoxin-cytotoxic moiety complexes to neuroectodermal tumor tissue correlates with therapeutic activity.

Furthermore, the present specification includes relevant *in vitro* and *in vivo* evidence incorporated by reference from the two applications to which it claims priority (*i.e.*, Appln. No.

08/774,154, which issued as U.S. Pat. No. 5,905,027 and Appln. No. 09/296,031, which issued as U.S. Pat. No. 6,667,156) (see first paragraph of page 48 of the Application, as filed). The present Specification incorporates by reference the entire contents of U.S. Pat. No. 5,905,027, including Examples 17, 21, and 23 of this patent. Example 17 shows tumor-selective accumulation of ^{131}I-TM-601, a chemically synthesized form of chlorotoxin, covalently linked to iodine 131 injected into the cerebrum of a mouse in which glioma was induced in the right brain 14 days earlier by intracranial injection of D54MG glioma cells, thereby demonstrating selective uptake of a chlorotoxin-cytotoxic moiety complex in an *in vivo* animal model for glioma. Example 21 shows that chlorotoxin radiolabeled with iodine 125 binds to glioma cells (D54MG glioblastoma cells) with high affinity and selectivity. Based on these results, an assertion is made that chlorotoxin "is glioma specific" and that chlorotoxin "with radioactive moieties can be used to treat gliomas" since "the molecule would selectively bind to gliomas and expose cells to high levels of radiation" (see last sentences of Example 21 of U.S. Pat. No. 5,905,027). Example 23 shows that treating glioma cells with a chlorotoxin-GST fusion protein attached to the cytotoxic moiety saporin (through a mouse anti-GST monoclonal antibody and then a goat anti-mouse antibody conjugated to saporin) results in a significant and selective killing of the glioma cells, which was not observed in control experiments.

Thus, the present Specification itself includes at least as much information as was found to be sufficient to support patentability in *Brana*.

Furthermore, Applicant submits herewith a Declaration executed by Douglas Jacoby, Ph.D., Senior Director of Research and Development of TransMolecular, Inc., Cambridge, Massachusetts, the assignee of the present Application. This Declaration presents results of clinical trials using ^{131}I-TM-601, confirming assertions made in the Specification. More specifically, the results show that a chlorotoxin-cytotoxic moiety complex (1) selectively reaches its target tumor site when administered to a patient either through intracranial or intravenous administration; (2) passes through the blood-brain barrier to reach a tumor located in the brain; and (3) has a therapeutic effect *in vivo*. Furthermore, intravenous administration of the chlorotoxin complex was found to result in selective uptake in glioma and metastatic melanoma, two of the claimed neuroectodermally-derived tumors.

The Jacoby Declaration therefore confirms that chlorotoxin linked to a cytotoxic moiety is indeed effective in the treatment of neuroectodermal tumors. Such a demonstration is not, of course, required for patentability (recall the court's comment in *Brana* that patentability is achieved "even though it may eventually appear that the compound is without value in the treatment of humans"), but nonetheless is presented to remove all doubt that the teachings of the present Specification do indeed correlate with pharmaceutical activity in humans.

Thus, for all the reasons mentioned above, Applicants submits that the Specification, as filed, and the Declaration by Dr. Jacoby provide more evidence than what has been deemed sufficient by the court *In re Brana* to establish the invention's asserted utility. At least 5 chlorotoxin complexes (TM-602, *i.e.*, chlorotoxin covalently linked to biotin; TM-601 radiolabeled with ^{131}I; chlorotoxin radiolabeled with ^{125}I; chlorotoxin-GST fusion protein; and chlorotoxin-GST fusion protein attached to saporin) have been tested and showed neuroectodermal tumor-selective binding/uptake in at least one *in vitro* or *in vivo* system. *In vitro* systems tested include glioma cells (D54MG glioblastoma cells) and non-tumor human astrocytes; and frozen or paraffin sections of human biopsy tissues including tissues from all claimed neuroectodermally-derived tumors. *In vivo* systems tested include mice in which glioma was induced in the right brain by intracranial injection of D54MG glioma cells. In addition, results of clinical trials using TM-601 radiolabeled with ^{131}I are provided that confirm the invention's asserted utility.

Having soundly established that the present Specification fully meets the legal requirements for patentability, Applicant now addresses some of the specific comments made by the Examiner in rejecting the claims.

In the Office Action, the Examiner has questioned whether a chlorotoxin fused to a cytotoxic moiety can pass through the blood-barrier in a subject and reach a target tumor located in the brain. The Examiner acknowledges that Veiseh teaches using near infrared (NIR) chlorotoxin-based probe to detect medulloblastoma tumors after systemic administration of the probe in 2 mouse models without surgical disruption of the blood-brain barrier. Yet, the Examiner questions whether other chlorotoxin agents (specifically chlorotoxin fused to a cytotoxic moiety) could similarly pass through the blood brain barrier.

Applicant respectfully points out that the Examiner's position is backwards. When the evidence of record indicates that a chlorotoxin agent *does* pass through the blood brain barrier, on what basis does the Examiner *assume* that all other chlorotoxin complexes *cannot* pass through the blood-brain barrier? The Examiner provides no evidence that one of ordinary skill in the art would doubt that other chlorotoxin agents would behave like the Veiseh agent. Indeed, as already mentioned above, Dr. Jacoby's Declaration confirms (with evidence from a clinical trial!) that TM-601 radiolabeled with iodine 131 *does* pass through the blood-brain barrier and reaches tumors located in the brain after intracranial or intravenous administration to provide therapeutic effect.

Additionally, in the Office Action, the Examiner has questioned whether a chlorotoxin-cytotoxic moiety complex could be used to treat different neuroectodermal tumors that differ from each other physiologically, morphologically and pathologically. Applicant respectfully submits that the Application, as filed, contains more than 18 examples of selective binding of TM-601 (as defined above) to different claimed neuroectodermally derived tumors, including *each and every one* of the tumor types recited in claim 16-20. Given that the specification established a correlation between binding and activity *in vivo,* and further that the Jacoby Declaration confirms therapeutic effectiveness in humans, these data are more than sufficient to support the breadth of the claim.

In the Office Action, the Examiner acknowledges that the phrase "cytotoxic moiety" is very broad and encompasses any protein or peptide or any molecule that is cytotoxic. The Examiner then states that "therefore the claims encompass using proteins or peptides having unknown amino acid sequences and biological functions". The Applicant respectfully disagrees with this statement. All of the cytotoxic moieties have a *known* biological function (whatever their chemical structure/amino acid sequence), and it is the same biological function: they are cytotoxic. As discussed above, the Specification specifically exemplifies the effectiveness of at least two different cytotoxic moieties, ^{131}I and saporin, and demonstrates that, notwithstanding their difference in chemical structure, their common activity is sufficient for their use in accordance with the present invention.

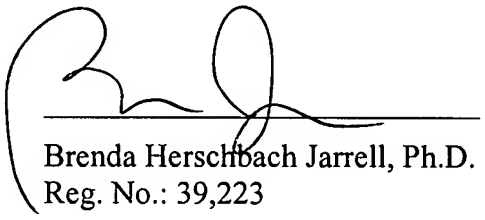
For all of the reasons set forth above, Applicant respectfully submits that the present Specification is fully supportive of the claims and meets the legal requirements for patentability. Therefore, Applicant respectfully requests that the rejection be removed or reconsidered.

CONCLUSION.

Applicant again thanks the Examiner for his careful review of the case. The claims have been amended to obviate all rejections. Based on the Remarks presented above, Applicant respectfully submits that Claims 1 and 15-28 are now in condition for allowance. A Notice to this effect is respectfully requested.

Please charge any fees that may be associated with this matter, or credit any overpayments, to our Deposit Account No.: 03-1721.

Respectfully submitted,



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